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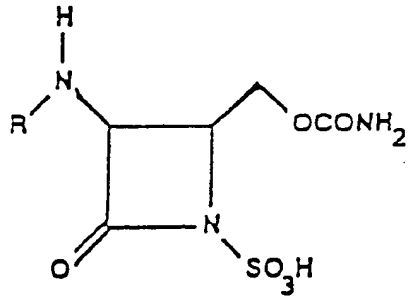
(54) Title: A PROCESS FOR THE PREPARATION OF 3-ACYLAMINO-4-CARBAMOYLOXYMETHYL-2-AZETIDINONE-1-SULPHONIC ACIDS AND INTERMEDIATES FOR THE PREPARATION THEREOF



(I)

(57) Abstract

A process for the preparatin of monolactams of formula (I) where R is acyl and of the pharmaceutically acceptable salts thereof, starting from (R) malic acid esters, through the new intermediate (3S, 4S) 3-hydrazino-4-hydroxymethyl azetidinone. Further, the conversion of (3S, 4S) 3-(benzyloxycarbonyl)amino-4-hydroxymethyl-2-azetidinone and (3S, 4S) 3-(tert-butoxycarbonyl)amino-4-hydroxymethyl-2-azetidinone into (3S, 4S) 3-(benzyloxycarbonyl)amino-4-(carbamoyloxy)-2-azetidinone and (3S, 4S) 3-(tert-butoxycarbonyl)amino-4-(carbamoyloxy)-2-azetidinone, respectively, is described.

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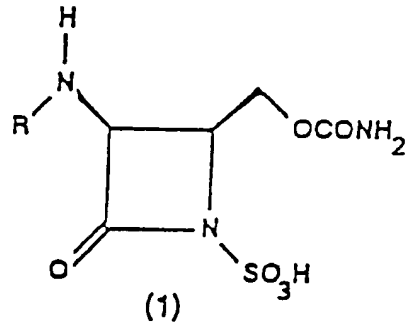
A PROCESS FOR THE PREPARATION OF 3-ACYLAMINO-4-CARBAMOYLOXYMETHYL-2-AZETIDINONE-1-SULPHONIC ACIDS AND INTERMEDIATES FOR THE PREPARATION THEREOF

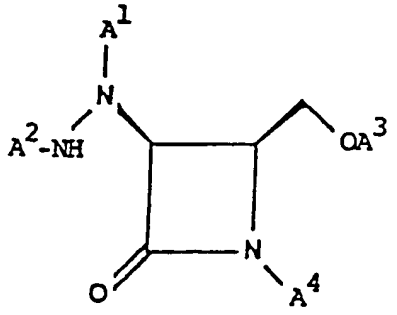
The present invention relates to a process for the synthesis of monobactams of formula (1)



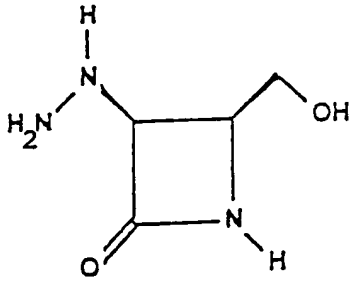
(1)

wherein R represents an easily removable or pharmaceutically acceptable acyl residue, and of pharmaceutically acceptable salts thereof, starting from (R) malic acid esters. Particularly, R represents the acyl residue of O-benzylcarbonic, O-tert-butylcarbonic, phenylacetic, phenoxyacetic, 2-(2-amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetic, 2-(2-amino-4-thiazolyl)-2-(Z)-(carboxymethoxyimino)acetic, 2-(2-amino-4-thiazolyl)-2-(Z)-(1-carboxy-1-methyl-ethoxyimino)acetic acids.

Further, the invention relates to intermediates, which are useful for the process, of the following formula



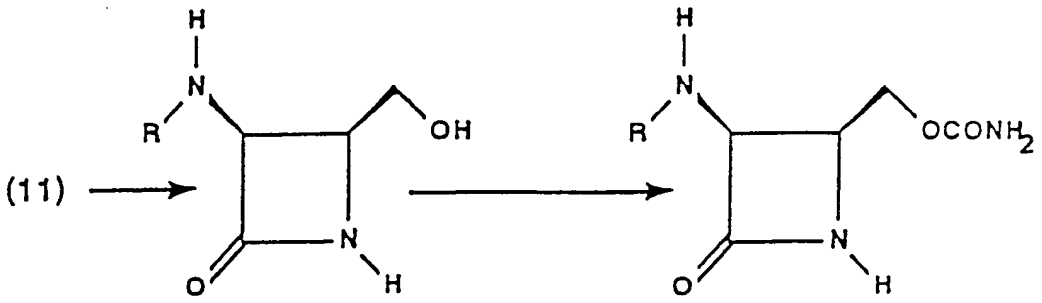
wherein A^1, A^2 and A^3, which are the same or different, represent hydrogen or nitrogen and oxygen protective groups, A^4 represents hydrogen, hydroxy or an OR^1 residue, wherein R^1 is methyl or arylalkyl group. Particularly, object of the present invention are (3S, 4S) 3-hydrazino-4-hydroxymethyl-2-azetidinone of formula (11)



(11)

and the inorganic and organic salts thereof.

The present invention further relates to the conversion of (11) into the well-known intermediates (3S, 4S) 3-(benzyloxycarbonylamino)-4-hydroxymethyl-2-azetidinone (13) and (3S, 4S) 3-(tert-butoxycarbonylamino)-4-hydroxymethyl-2-azetidinone (14), as well as to the conversion of said compounds (13) and (14) into the corresponding intermediates (3S, 4S) 3-(benzyloxycarbonylamino)-4-carbamoyloxymethyl-2-azetidinone (15) and (3S, 4S) 3-(tert-butoxycarbonylamino)-4-carbamoyloxymethyl-2-azetidinone (16), the former, which is already well-known, can be converted, with well-known procedures, into monobactams (1)



(13) : R= $PhCH_2OCO$
(14) : R= $(CH_3)_3COCO$

(15) : R= $PhCH_2OCO$
(16) : R= $(CH_3)_3COCO$

PRIOR ART

The discovery of antimicrobial compounds, named monobactams or sulfazecins, which are characterized by a 2-azetidinonic structure bearing an acylamino group at the 3-position and a sulfonic acid group at the 1-position [R.B. Sykes et al., Nature, 291, pag. 489 (1981); A. Imada et al., Nature, 291, pag. 590 (1981)] opened a wide line of research and many non-natural derivatives of said class have subsequently been prepared by synthetic route. Particularly, several monobactams of general formula (1) and the pharmaceutically acceptable salts thereof showed a remarkable antibiotic activity towards gram-negative bacteria, Pseudomonas aeruginosa included, as well as a consistent stability towards ß-lactamases, which make them particularly interesting from a pharmacological point of view (WO 81/00103; WO 81/00183; WO 81/00252; EP-73061; US 4.572.801; 4.665.067; 4.673,739; 4.675.397; 4.782.147; 4.882.788; S. Kishimoto, et al., J. Antibiot., 36, pag. 1421 (1983)).

There is no convenient manner to obtain said monobactams through a microbiological route. Moreover,

it has been verified that only the compounds with (3S) configuration are active and that the cis derivatives (namely (4S)) are more active than the trans derivatives. Therefore, the preparation thereof requires a stereoselective (or a diastereospecific), and enantioselective (or enantiospecific) synthesis, otherwise, in the event of a synthesis leading to racemic products, an optical resolution.

Some syntheses of the compounds of general formula (1) have been described. Said compounds are prepared starting from optically pure natural compounds, such as ascorbic acid (C.C. Wei, et al., J. Org. Chem., 50, 3462 (1985)), or D-glyceraldehyde (A.K. Bose, et al., J. Chem. Soc., Chem. Commun., 161 (1986)), or aspartic acid (Y. Takahashi, et. al., Chem. Pharm. Bull., 34, 2732 (1986)) or by 2+2 cycloaddition between imines and carboxylic derivatives in the presence of chiral promoters on one of the two substrates (S. Cardani et al., Tetrahedron, 5563 (1988); D.A. Evans, E.B. Sjogren, Tetrahedron Lett., 26, 3783 (1985); R.C. Thomas, Tetrahedron Lett., 5239 (1989)).

Object of the present invention is a totally synthetic process for the preparation of the above compounds of formula (1). The process of the invention is carried out starting from (R) malic acid esters, which are easily obtained from L-tartaric acid.

The compounds of formula (1) are obtained with the correct relative and absolute configuration by means of the process of the invention in a simple and industrially applicable way.

DETAILED DISCLOSURE OF THE INVENTION

Scheme 1 and Scheme 2 illustrate a preferred embodiment of the invention.

In said Schemes:

- X is a convenient protective group, which is compatible with reaction conditions. Said protective group can be removed at the step wherein compound (7) is obtained. The removal of X can be carried out before, after or simultaneously the removal of OR^1 group, in reaction conditions compatible with other functional groups present in the compound.

Example of X are $R^4R^5R^6Si$ or $R^4R^5R^6SiCH_2CH_2OCH_2$ groups, where R^4, R^5 and R^6 are alkyl, aryl or alkoxy groups. Examples of R^4, R^5 and R^6 are Ph_2tBuSi; $CAr^1Ar^2Ar^3$, where Ar^1, Ar^2, Ar^3 represent substituted or unsubstituted, optionally linked each other, aromatic residues (such as triphenylmethyl); CH_2OCH_2Ar, where Ar represents a substituted or unsubstituted aromatic residue (for example $PhCH_2OCH_2$).

- Y is a C_1-C_3 alkyl group, such as methyl, ethyl, n-propyl; methyl group being preferred.

- R^1 is a methyl group, or a CH_2Ar group, where Ar is as above defined; for example benzyl group.

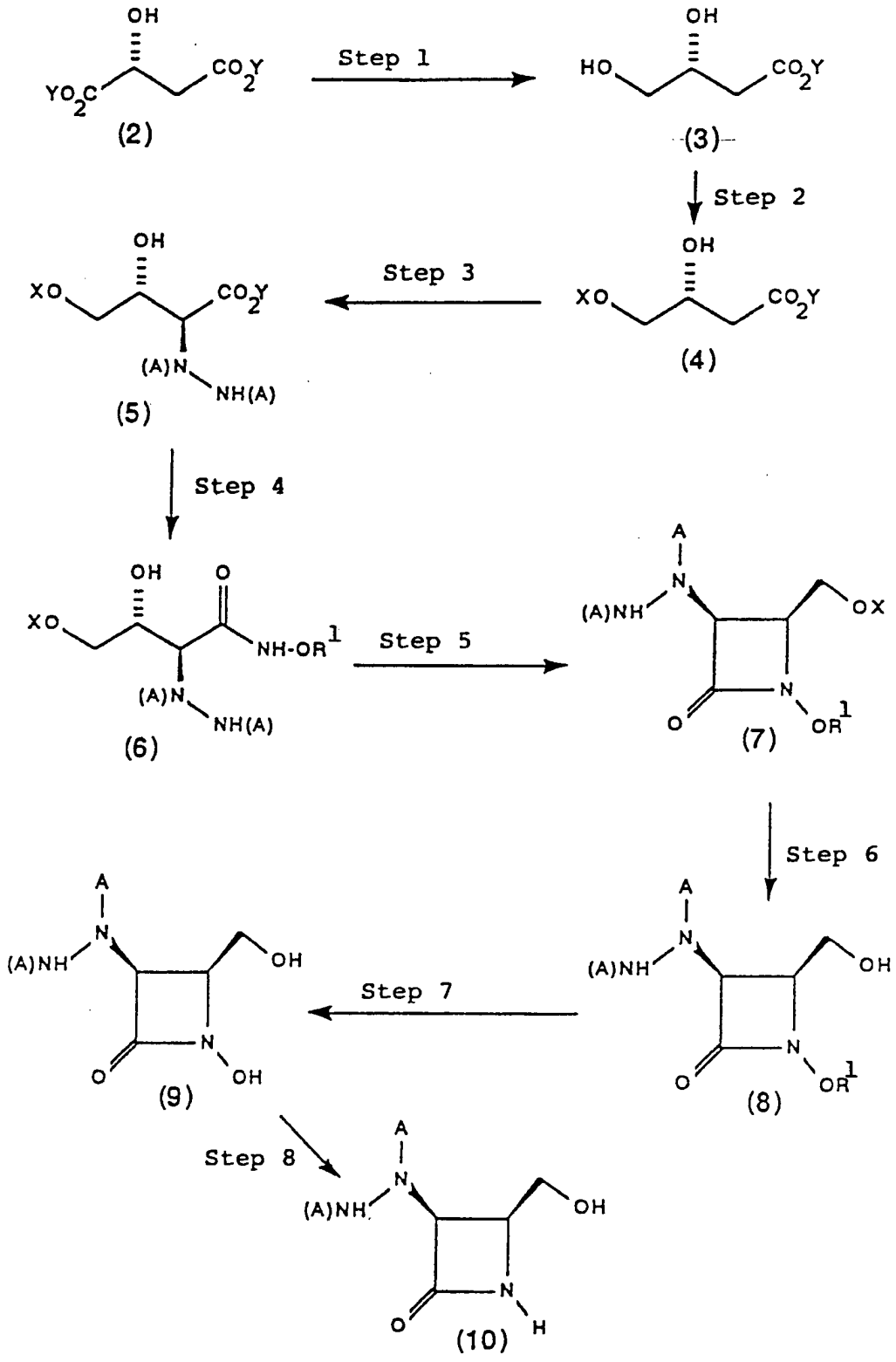
- A is a tert-butoxycarbonyl or arylalkyloxycarbonyl group.

- R is an easily removable or pharmaceutically acceptable acyl group, particularly the acyl residue of O-benzylcarbonic, O-tert-butylcarbonic, phenylacetic, phenoxyacetic, 2-(2-amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetic, 2-(2-amino-4-thiazolyl)-2-(Z)-(carboxymethoxyimino)acetic, 2-(2-amino-4-thiazolyl)-2-(Z)-(1-

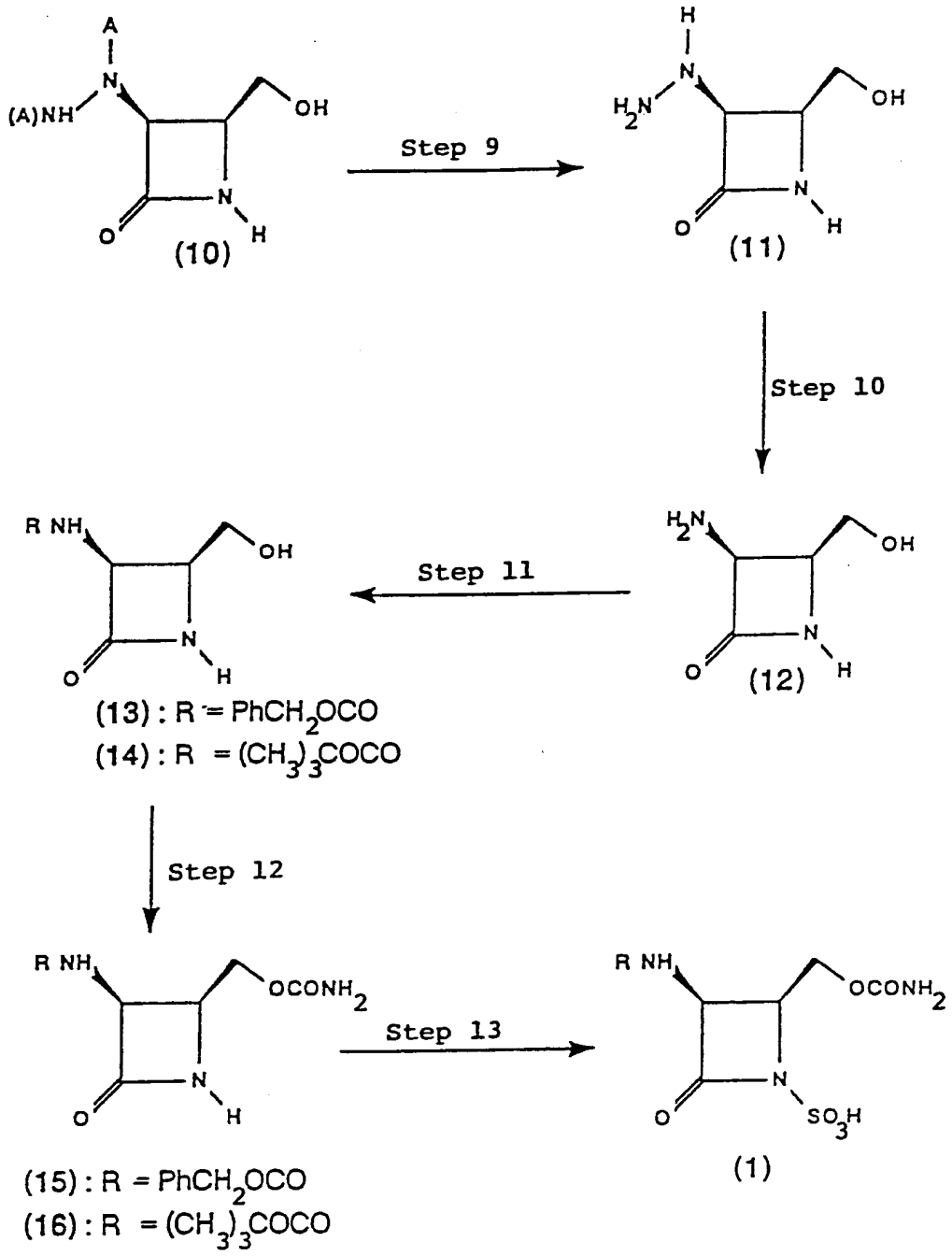
carboxy-1-methyl-ethoxyimino)acetic acids.

The compounds of formula (I) can also be in the form of pharmaceutically acceptable salts, and the compound of formula (II) can also be in the form of an hydrazinium salt.

SCHEME 1


OH
CO2Y
YO2C
(2)
Step 1
HO
(3)
Step 2
XO
(4)
Step 3
(A)N
NH(A)
(5)
Step 4
O
NH-OR1
(6)
Step 5
A
(A)NH
OX
(7)
Step 6
OH
(8)
Step 7
(9)
Step 8
(10)
H

SCHEME 2


A
(A)NH
N
OH
O
N
H
(10)
Step 9
H
N
H2N
OH
O
N
H
(11)
Step 10
H2N
OH
O
N
H
(12)
Step 11
R NH
OH
O
N
H
(13) : R = PhCH2OCO
(14) : R = (CH3)3COCO
Step 12
R NH
OCONH2
O
N
H
(15) : R = PhCH2OCO
(16) : R = (CH3)3COCO
Step 13
R NH
OCONH2
O
N
SO3H
(1)

As previously mentioned, Schemes 1 and 2 represent only one among the many other possible embodiments of the process according to the invention, in fact R^2 acyl residues can be different from the ones above mentioned.

Referring to Scheme 1, the preparation starts from a (R) malic acid ester (2), which is converted into the diol (3) (step 1) by regioselective reduction with borane and sodium borohydride, as described by S. Saito, et al., (Chem. Lett., 1389 (1984)).

Subsequently, the diol (3) can selectively be protected at the primary hydroxy group: reaction conditions vary according to the protective group being used. For $R^4R^5R^6Si$ type groups, the protection is carried out by reacting the corresponding halides in a dipolar aprotic solvent, such as dimethylformamide or dimethyl sulfoxide, at a temperature ranging from 0°C to 70°C, preferably from 20°C to 50°C, in the presence of a base such as a tertiary amine, or pyridine or imidazole; particularly, in the case of X = Ph_2t-BuSi, said reaction is preferably carried out in dimethylformamide at 25°C, in the presence of imidazole, as described by G. Guanti, L. Banfi, E. Narisano, (Tetrahedron Lett., 30, 5507 (1989)).

When X = $R^4R^5R^6SiCH_2CH_2OCH_2$ or CH_2OCH_2Ar, the reaction is preferably carried out in a chlorinated solvent (for example, methylene chloride) in the presence of a tertiary amine (for example diisopropylethylamine) at a temperature ranging from 0°C to the solvent boiling temperature.

When X = $CAr^1Ar^2Ar^3$, the protection is carried out

in a halogenated solvent, such as, for example, methylene chloride, by treating with the appropriate halide, in the presence of a nitrogen base (for example, pyridine) and at a temperature ranging from 0°C to the solvent boiling temperature. Particularly, when X = triphenylmethyl, the protection reaction has already been described in literature (K. Prasad, et al., Tetrahedron: Asymmetry , 307 (1990)).

The compounds of formula (4) are obtained with very good protection yield by using X = $CAr^1Ar^2Ar^3$ or X = $R^4R^5R^6Si$, whenever R^4, R^5 and R^6 are sufficiently bulky.

Next step consists in condensing ß-hydroxyesters (4) with a di-t-butyl- or diarylalkyl azodicarboxylate. Said transformation can be carried out by treating a compound (4) with at least two equivalents of a strong base, such as, for example, a lithium or sodium or potassium dialkylamide (for example, diisopropylamide) in an aprotic solvent, such as tetrahydrofurane or dimethoxyethane, at a temperature ranging from -78°C to 20°C, preferably from -40°C to 0°C, followed by the reaction with the azodicarboxylate, at a temperature ranging from -78°C to 0°C. Yields and diastereoselectivity depend on the kind of the protective group X and on reaction temperature. Good results are obtained using X = trityl, and carrying out enolate formation at -40°C and condensing between -40°C and 0°C. In said conditions, a clear prevalence of (2S, 3R) anti-diastereoisomer, with diastereoisomeric ratio higher than 9:1, is reported and main diastereoisomer yield is about 50%. When X = Ph_2t-BuSi, said condensation had

already been described (G. Guanti et al., Tetrahedron Lett., 30, 5507 (1989)) and resulted in lower stereoselectivity and with a slightly lower adduct yield.

The so obtained products (5) are isolated by chromatography or crystallization.

Next step consists in converting the esters (5) into O-alkylhydroxamates (6). Said conversion can be effected in two ways.

A) A two-step way. The first step consists in transforming the ester group into an acid one. This can be accomplished by treating with an excess of a 0,1 to 2 N alkali hydroxide solution, such as lithium, sodium, potassium, etc, hydroxide in water, in the presence of one or more organic water-miscible cosolvent, such as methyl or ethyl alcohol, tetrahydrofurane, dioxane, dimethylformamide, acetonitrile, etc, or in an alcoholic solvent, such as methyl or ethyl alcohol, at a temperature ranging from -20°C to 60°C, preferably from 0°C to 40°C. The best results are obtained when X = $CAr^1Ar^2Ar^3$ or X = $R^4R^5R^6SiCH_2CH_2OCH_2$ or CH_2OCH_2Ar. The so obtained carboxylic acids can be isolated by extraction or by treating with an appropriate ion exchange resin and subsequent by purificating by crystallization or chromatography. Alternatively, the basic solution containing the carboxylic acid salts can be used as such for the next reaction.

The second step consists in coupling the so obtained acids (or the salts thereof) with the appropriate O-alkylhydroxylamine (or a hydroxylammonium salt thereof). Said step can be carried out both starting from the carboxylic acids and starting from

the crude carboxylate solution, which has previously been obtained by the above saponification.

Starting from the carboxylic acids, the coupling can be executed in an aqueous solution containing an appropriate water-soluble cosolvent, such as tetrahydrofurane, dimethylformamide or acetonitrile, keeping pH between 4 and 7, according to the group X present, by reacting with the appropriate O-alkylhydroxylamine (or a salt thereof) (for example 1-2 equivalents), in the presence of a condensing agent, such as, for example, N,N'-dicyclohexylcarbodiimide (DCC) or 1-(3-diaminopropyl)-3-ethylcarbodiimide (WSC) (1-3 equivalents). Otherwise, the coupling can also be carried out activating the purified carboxylic acids by reaction with dicyclohexylcarbodiimide and N-hydroxybenzotriazole in a dipolar aprotic solvent, such as acetonitrile, dioxane, tetrahydrofurane or dimethylformamide and reacting the so activated adducts in the same solvent with the appropriate O-alkylhydroxylamine or a hydroxylammonium salt thereof (in the latter case also adding an equivalent amount of a tertiary amine, such as, for example, triethylamine).

Further, the same coupling can directly be performed by using the crude alkali carboxylate solution, which has been obtained, as above described, from C_1-C_3 alkyl ester saponification. After acidifying to a pH between 3 and 8, the coupling can be performed by reacting with the appropriate O-alkylhydroxylamine (or a hydroxylammonium salt thereof) in the same solvent wherein saponification was carried out, optionally integrated with the addition of water or of

appropriate organic cosolvents, such as dimethylformamide or tetrahydrofurane, in the presence of a condensing agent such as, for example, N,N'-dicyclohexylcarbodiimide (DCC) or 1-(3-diaminopropyl)-3-ethylcarbodiimide (WSC) (1-3 equivalents). For example, when X = triphenylmethyl, the coupling is directly performed on the lithium carboxylate dissolved in a tetrahydrofurane-water mixture using O-benzylhydroxylamine, lithium hydroxide as the base, WSC as the condensing agent. A 50-60% yield is obtained.

B) A one-step way. The esters (5) can be transformed into hydroxamates (6) in a single step by reacting them with the adduct which has been obtained by mixing the appropriate O-alkylhydroxylamine with trimethylaluminum in an aprotic solvent, such as, for example, tetrahydrofurane, at a temperature ranging from -20°C to the solvent boiling temperature (preferably from 0°C to 20°C).

Next step, which consists in transforming hydroxamates (6) into ß-lactams (7), can be performed in an appropriate organic solvent (for example tetrahydrofurane, acetonitrile or dimethylformamide) preferably by treating with triphenylphosphine and a dialkyl azodicarboxylate (such as a diethyl or diisopropyl azodicarboxylate), or by treating with triphenylphosphine, carbon tetrachloride and triethylamine at a temperature ranging from 0°C to 60°C (preferably from 20°C to 30°C). Alternatively, the same transformation can be carried out by converting the alcohol into an alkansulfonyl derivative by treating, for example, with methanesulfonyl chloride in pyridine, followed by treatment

with bases, such as sodium hydrogencarbonate or sodium carbonate in dipolar aprotic solvents, such as acetone, dioxane, etc. The products (7) are purifiable by means of extraction, chromatography or crystallization.

For example, when X = triphenylmethyl and R^1 = benzyl, the conversion, which is carried out with diethyl azodicarboxylate and triphenylphosphine in tetrahydrofurane at room temperature, occurs with very good yields (about 95%).

The conversion of ß-lactams (7) into compounds (10) can be accomplished in several ways. The choice of the method to be used depends on the nature of the X and R^1 groups.

In fact, in some cases it is convenient to remove the X protective group before R^1O group; in other cases it is convenient to act contrarily; finally, in some cases it is possible to remove the two groups at the same time. When X = $R^4R^5R^6Si$ or $R^4R^5R^6SiCH_2CH_2OCH_2$ (for example Ph_2t-BuSi, $Me_3SiOCH_2CH_2OCH_2$), protective group removal can be performed both before and after removing OR^1 group (preferably before), by treatment with a fluoride (for example tetra-n-butylammonium fluoride) in a solvent, such as tetrahydrofurane or dioxane. When X = $CAr^1Ar^2Ar^3$, protective group removal is preferably performed before OR^1 group removal to give the derivatives (8). Said unblocking can be made, for example, by treating with a strong protic acid (such as a sulfonic acid or trifluoroacetic acid) in methyl or ethyl alcohol at a temperature ranging from 0°C to 60°C, or by heating, at a temperature ranging from 20°C to 100°C, in an acetic acid-water mixture. When X =

CH_2OCH_2Ar and R^1 = CH_2Ar both groups can be removed at the same time to give the product (9) directly. When X is above (CH_2OCH_2Ar) and R^1 is methyl, then X group is removed before R^1 group to give (8). In both cases, deprotection can be performed by hydrogenating in an appropriate solvent (for example, methyl, ethyl, n-propyl, iso-propyl alcohol or ethyl acetate) in the presence of a transition metal catalyst, such as palladium (for example, pure or supported on carbon or barium sulfate) or platinum (for example, pure or in the form of dioxide), at a pressure ranging from 1 to 10 atmospheres.

The products (8) (R^1 = CH_2Ar) can be converted into the compound (9) by hydrogenating in an appropriate solvent (for example, methyl, ethyl, n-propyl, iso-propyl alcohol or ethyl acetate) in the presence of a transition metal catalyst, such as palladium (for example, pure or supported on carbon or barium sulfate) or platinum (for example, pure or in the form of dioxide), at a pressure ranging from 1 to 10 atmospheres. For example, very high yields are obtained by operating in methyl alcohol at 1 atmosphere pressure and using 10% palladium on carbon as catalyst. The so obtained hydroxamic acid (9) requires no further purification, but it can directly be used for the next step, which consists in reducing it to give the azetidinone (10).

Said transformation can be performed, for example, by adding a aqueous hydrochloric acid titanium trichloride solution to the substrate (9), which is dissolved in a water/alcohol system (for example

water/methanol) at a pH between 3 and 10 (preferably 7), maintained with buffer solutions, or by simultaneously dropping an alkali hydroxide solution. In said conditions, good yields, about 50-60%, are obtained.

When R^1 = methyl, the products (8) can directly be converted into (10) in a single step, by treating them with alkali metals (for example, sodium) in liquid ammonia, optionally in the presence of organic cosolvents.

Finally, when R^1 = methyl and X = $ArCH_2OCH_2$ or = $Ar^1Ar^2Ar^3C$, (7) can also be converted directly into (10) in a single step, by treating (7) with alkali metals (for example, sodium) in liquid ammonia, optionally in the presence of organic cosolvents. The compound (10) can be purified by chromatography or crystallization.

Next step consists in converting (10) into the key intermediate (11) and can be carried out by treating (10) with a strong carboxylic acid, such as, for example, trifluoroacetic or formic acid. A cosolvent, which is compatible with reaction conditions, for example, methylene chloride, can optionally be used. Said reaction can be carried out with very good yields, by stirring for 1 hour a 1:1 trifluoroacetic acid: methylene chloride solution of (10), at a temperature ranging from 0°C to 25°C. The so obtained product (11) can be used wether as such for the next reaction, or purified by the conventional techniques (crystallization, ion exchange chromatography, etc.).

The product (11) and the hydrazinium salts thereof

(for example, chloride, acetate, trifluoroacetate, formate) are new, therefore they are a further object of the present invention.

(11) can be converted into the known intermediate (12) by reacting a hydrazinium salt thereof with hydrogen in the presence of catalysts, such as platinum dioxide or Raney® Nickel, at a pressure ranging from 1 to 200 atmospheres and, depending on the used catalyst, in water, alcohol (for example, methanol or ethanol) or water-alcohol mixtures. Also (12) can be wether purified or directly reacted, as crude, with benzyloxy-carbonyl chloride or with di-t-butyl dicarbonate to give the known products (13) and (14). This last conversion can be performed by treating with the appropriate acylating agent in an anhydrous solvent, such as dimethylformamide or acetonitrile and in the presence of a base, such as a tertiary amine (for example, triethylamine); otherwise, and preferably, in an aqueous solution kept at a pH between 8 and 10 with alkaly hydroxides (lithium, sodium or potassium) or alkali carbonates (sodium, potassium). As above stated the products (12), (13) and (14) are known even if they have been prepared through a different synthetic route (R.C. Thomas, Tetrahedron Lett., 5239 (1989)).

The products (13) and (14) can be transformed into the carbamates (15) and (16), the former being a well known derivative (U.S. 499,801; S. Kishimoto, et al., J. Antibiot., 36, pag. 1421 (1983)). Said conversion is new, therefore it is a further object of the present invention.

It can be performed by reacting (13) or (14) with

an acyl or sulfonyl isocyanate in an aprotic solvent, such as dimethylformamide or methylene chloride or tetrahydrofurane, followed by the resulting N-acyl (or N-sulfonyl) carbamate deprotection. In the case of N-chloracetylcarbamates, said deprotection can be performed by treatment with sodium or potassium N-alkyl dithiocarbamates, while, in the case of N-sulfonylcarbamates, by treatment with sodium sulfite. Very good results (with overall yield of the two steps comprised between 50% and 75%) are obtained, for example, by carrying out the reaction with chloroacetyl isocyanate in dimethylformamide/methylene chloride at 0°C and by deprotecting the chloroacetyl urethane by reacting with sodium N-methyl dithiocarbamate.

Compound (15) can be converted by means of well-known techniques (U.S. Patent Application 499,801; S. Kishimoto, et al., J. Antibiot., 36, pag. 1421 (1983)), into the products of general formula (1).

According to a further embodiment of the present invention, the above process can be alternatively carried out as far as the introduction of amino group into 2-position of ß-hydroxyester (4) is concerned, by electrophilic amination with other synthetic equivalents of NH_2^+ group, such as sulfonyl azides, O-substituted hydroxylamines and diazonium salts. According to the invention, sulfonyl azides, especially p-toluensulfonyl azide, 2,4,6-triisopropylbenzensulfonyl azide and p-dodecylbenzensulfonyl azide, are particularly preferred.

The following examples further illustrate the invention.

EXAMPLE 1

Methyl (3R) 3-hydroxy-4-(triphenylmethyl)oxybutanoate (4) (X = triphenylmethyl; Y = Me) from (3).

12.96 g (96.62 mmoles) of (3), wherein Y = Me, were dissolved in 200 ml of anhydrous methylene chloride, under nitrogen stream, and cooled to 0°C. 11.72 ml (144.93 mmoles) of pyridine and 32.32 (115.92 mmoles) of trityl chloride were added; after 15 minutes the ice bath was removed and the reaction was let to stand under stirring at r.t. for 20 hours. As the reaction resulted incomplete, 3 ml (3.71 mmoles) of pyridine and 8 g (2.87 mmoles) of trityl chloride were further added, and the reaction was carried out for further 3 hours. The suspension was diluted with brine and extracted 3 times with diethyl ether; then the organic phase was dried over Na_2SO_4 and vacuum distilled; residual pyridine was removed by azeotropic evaporation after adding 200 ml of benzene. The crude was purified through a 500 g SiO_2 column, with a gradient eluent (8:2:0.1 to 3:7:0.1 petroleum ether/diethyl ether/triethylamine).

28.69 g (yield 79%) of product, which was crystallized from isopropyl ether/penthane to a colourless compound, were obtained.

^{1}H-NMR ($CDCl_3$; 200 MHz; J(Hz)): δ_H 7.23-7.46 (15 H, m, trityl), 4.23 (1H, center of m, H-3), 3.68 (3H, s, OCH_3), 3.17 (2H, d, J 5.4, H-4), 2.90 (1H, d, J 4.7, OH), 2.53 e 2.57 (2H, AB portion of ABX syst., J_{AB} 14.7, J_{AX} 3.6, J_{BX} 9.2, H-2).

IR (chloroform, cm^{-1}): ν 1728 (ester carbonyl).

M.P. 71.8-72.6°C (iso-propyl ether/penthane).

$[\alpha]_D^{13}$ = +5.48° (c 1.99, chloroform).

Elemental analysis for $C_{24}H_{24}O_4$; found: C 76.54%; H 6.27%; O 17.19%; calculated: C 76.57%; H 6.43%; O 17.00%.

EXAMPLE 2

Methyl (2S, 3R) 2-[N,N'-bis-(tert-butoxycarbonyl)hydrazino]-3-hydroxy-4-(triphenylmethyl)oxybutanoate (5) (X = triphenylmethyl; Y = Me) from (4).

9.16 ml (65.34 mmoles) of diisopropylamine were added, under nitrogen stream, to 80 ml of anhydrous tetrahydrofurane (THF) and the solution was cooled down to -18°C; 38.29 ml (61.26 mmoles) of n-BuLi (1.6 M hexane solution) were subsequently dropped and the solution was kept under stirring at the same temperature for 20 minutes. The reaction was then cooled to -40°C and 7.687 g (20.42 mmoles) of (4), obtained in example 1, previously dissolved in 20 ml of THF, were added. After 5 minutes, the reaction vessel was let reach 0°C and let under stirring for 30 minutes. After cooling again to -20°C, di-tert-butyl azodicarboxylate, previously dissolved in 20 ml of THF, was added and the system was kept under stirring, letting the temperature to raise till 0°C. The reaction was stopped at 0°C, by adding 7.5 ml of glacial acetic acid. After 5 minutes, the suspension was diluted with a NH_4Cl saturated solution and brine and extracted with diethyl ether.

The organic phase, previously dried over Na_2SO_4, was concentrated under reduced pressure, to give 17.53 g of a yellow oil, which was passed through a 350 g SiO_2 chromatographic column, eluting with a 8:2:0.03 to

5:5:0.03 petroleum ether/diethyl ether/triethylamine mixture. 5.82 g (yield 48%) of (5) were obtained.

^{1}H-NMR (DMSO-d_6, 80 MHz; 130°C; J(Hz)): δ_H 8.07 (1H, s broad, NH), 7.03-7.67 (15H, m, trityl), 4.86 (1H, d, J 6.5, H-2), 4.00-4.35 (1H, m, H-3), 3.61 (3H, s, OCH_3), 3.22 (2H, d, J 5.3, H-4), 1.44*[9H, s, N-(Boc)], 1.40*[9H, s, NH-(Boc)].

IR (chloroform, cm^{-1}): ν 1731 (ester carbonyl).

$[\alpha]_D^{13}$ = +18.73° (c 2.04, chloroform).

Elemental analysis for $C_{34}H_{42}N_2O_8$; found: C 67.04%; H 6.93%; N 4.74%; O 21.29%; calculated: C 67.31%; H 6.98%; N 4.62%; O 21.1%.

* interchangeable signals

EXAMPLE 3

Benzyl (2S, 3R) 2-[N,N'-bis-(tert-butoxycarbonyl)hydrazino]-3-hydroxy-4-(triphenylmethyl)oxybutanehydroxamate (6) (X = triphenylmethyl) from (5).

2.90 g (4.78 mmoles) of ester (5), obtained in example 2, were dissolved in 20 ml of freshly distilled THF, 30 ml of distilled water were then added and the system was cooled to 0°C; 31 ml (15.3 mmoles) of 0.5 N LiOH aqueous solution were dropped within 15'. The suspension was kept under vigorous stirring at r.t. for 7 hours. The reaction was cooled to 0°C and pH was adjusted to 6 with 1N HCl; 915 mg (5.74 mmoles) of O-benzylhydroxylamine were added and pH was adjusted to 6, adding a 0.5 N LiOH aqueous solution. Finally, 1.833 g (9.56 mmoles) of WSC (1-(3-diaminopropyl)-3-ethylcarbodiimide) were added and the system was let under stirring at r.t. for 20 hours. The aqueous phase was saturated with NaCl, then extracted with ethyl acetate.

The organic extract was dried over Na_2SO_4 and evaporated to dryness, giving 3.56 g of crude in the form of a foam. The crude was passed through a 150 g SiO_2 chromatographic column, eluting with a 6:4:0.03 to 4:6:0.03 petroleum ether/diethyl ethertriethylamine mixture. 1.994 g (yield 60%) were obtained.

^{1}H-NMR (DMSO-d_6, 80 MHz, 130°C, J(Hz)): δ_H 7.24-7.47 (20H, m, trityl and benzyl aromatics), 4.79 (2H, s, OCH_2Ph), 4.55 (1H, d, J 6.2, H-2), 4.11-4.31 (1H, m, H-3), 3.19-3.26 (1H, m, H-4), 1.40* (9H, s, N-(Boc)), 1.37* (9H, s, NH-(Boc)).

IR (chloroform, cm^{-1}): ν 1719, 1685, 1673 (carbonyl; hydroxamate and Boc).

$[\alpha]_D^{13}$ = -6.27° (c 2.41, chloroform).

* interchangeable signals

EXAMPLE 4

(3S, 4S) 1-benzyloxy-3-[N,N'-bis-(tert-butoxycarbonyl)hydrazino]-4-(triphenylmethyl)oxymethyl-2-azetidinone (7) (R^1 = benzyl) from (6).

2.950 g (4.67 mmoles) of (6), obtained in example 3, were dissolved in 25 ml of anhydrous THF and added, in nitrogen stream and r.t., to 1.837 g (7.01 mmoles) of triphenylphosphine and 1.10 ml (6.99 mmoles) of diethyl azodicarboxylate. The yellow solution was let under stirring for 15 hours; the solvent was then vacuum distilled and the residue was directly passed through a 200 g SiO_2 chromatographic column, eluting with a 7:3 to 1:1 petroleum ether/diethyl ether mixture. 2.730 g (95% yield) of a colourless foam were obtained.

^{1}H-NMR (DMSO-d_6, 80 MHz, 131°C, J(Hz)): δ_H 8.45 (1H, s

broad, NH), 7.24-7.50 (20H, m, trytil and benzyl aromatics), 4.99 (2H, s, OCH_2Ph), 4.84 (1H, d, J 5.6, H-3), 4.16 (1H, m center, H-4), 3.45-3.62 (2H, m, CH_2OH), 1.37*(9H, s, N-(Boc)), 1.27*(9H, s, NH-(Boc)).

IR (chloroform, cm^{-1}): ν 1783 (ß-lactam carbonyl), 1722 (Boc carbonyl).

$[\alpha]_D^{16}$ = +5.07° (c 1.96, chloroform).

Elemental analysis for $C_{40}H_{45}N_3O_7$; found: C 69.95%; H 6.75%; N 6.31%; O 16.99%; calculated: C 70.67%; H 6.67%; N 6.18%; O 16.47%.

* interchangeable signals

EXAMPLE 5

(3S, 4S) 1-benzyloxy-3-[N,N'-bis-(tert-butoxycarbonyl)hydrazino]-4-hydroxymethyl-2-azetidinone (8) (R^1 = benzyl) from (7).

1.045 g (1.54 mmoles) of (7) were dissolved in 20 ml of anhydrous methanol, under nitrogen stream; the solution was cooled to 0°C and 292 mg (1.54 mmoles) of p-toluensulfonic acid were added. After 5 minutes, the ice bath was removed and the system was let to stand under stirring at r.t. for 2.5 hours. Acid excess was neutralized with a $NaHCO_3$ saturated solution, then the solution was concentrated to a small volume. The residue was diluted with brine and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and the solvent was vacuum distilled. 1.067 g of crude were passed through a 40 g SiO_2 chromatographic column, using a 1:1 to 3:7 petroleum ether/diethyl ether mixture. 458 mg (70% yield) of a white foam were obtained.

^{1}H-NMR (DMSO-d_6, 80 MHz, 129°C, J(Hz)): δ_H 8.46 (1H, s

broad, NH), 7.28-7.40 (5H, m, benzyl aromatic), 6.91 (1H, s broad, OH), 5.00 (2H, s, OCH_2Ph), 4.92 (1H, d, J 5.4, H-2), 4.01-4.14 (1H, m, H-3), 3.62-3.99 (2H, m, CH_2-OH), 1.44*(9H, s, N-(Boc)), 1.40*(9H, s, NH-(Boc)).

$[\alpha]_D^{15}$ = +7.65° (c 2.01, chloroform).

Elemental analysis for $C_{21}H_{31}N_3O_7$; found: C 57.28%; H 6.96%; N 9.48%; O 26.28%; calculated: C 57.65%; H 7.14%; N 9.6%; O 25.6%.

* interchangeable signals

EXAMPLE 6

(3S, 4S) 3-[N,N'-bis-(tert-butoxycarbonyl)hydrazino]-4-hydroxymethyl-2-azetidinone (10) from (8) through intermediate (9).

175 mg of 10% Pd/carbon were added to a solution of 746 mg (1.71 mmoles) of (8), obtained in example (5), in 20 ml of methanol. The suspension was hydrogenated for 1 hour at r.t. and at atmospheric pressure. The catalyst was filtered through a paper filter and thoroughly washed with methanol; the filtrate was subsequently evaporated to dryness at reduced pressure giving (9) in the form of a colourless oil, which was immediately used for the next step. The crude from hydrogenation was dissolved in 8 ml of MeOH and added in a beaker containing 30 ml of phosphate buffer at pH 7. pH, which was monitored with a pH meter, was adjusted to 7 with the addition of 3N NaOH by means of a buret. 3.5 ml (8.55 mmoles) of a 30% $TiCl_3$ in 2N HCl solution were dropped, into the vigorously stirred solution within 15 minutes. In the meantime, pH was maintained the nearest to 7 with 3N NaOH additions (about 11 ml). At the end of $TiCl_3$ additions, the system was let to

stand under stirring, at r.t., for 2 hours. The aqueous system was saturated with NaCl, pH was adjusted to 8.5 and the stirring was continued for 1 day further, in order to allow the release of the product by Ti(III). The suspension was filtered on Celite® and the aqueous phase was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and the solvent was vacuum distilled.

The crude was passed through a 30 g SiO_2 chromatographic column, using a 8:2 ethyl acetate/petroleum ether mixture. 348 mg (63% yield; two steps) of a white solid, which crystallized spontaneously, were obtained.
^{1}H-NMR (DMSO-d_6, 80 MHz, 130°C, J(Hz)): Note: the spectrum gave poor resolution even at this temperature and some peaks resulted rather broadened; however, the spectrum was easier understandable when recorded in the presence of 5% D_2O; δ_H 4.90 (1H, m center, X part of ABCX syst., H-3), 3.52-3.79 (3H, m, ABC part of ABCX syst., H-4 + CH_2OH), 1.44 (18H, s, N(Boc) + NH(Boc)).
IR (chloroform, cm^{-1}): ν 1770 (ß-lactam carbonyl), 1722 (Boc carbonyl).
$[\alpha]_D^{18}$ = +16.4° (c 1.52, methanol).
Elemental analysis for $C_{14}H_{25}N_3O_6$; found: C 50.58%; H 7.41%; N 12.72%; O 29.29%; calculated: C 50.75%; H 7.6%; N 12.68%; O 28.97%.
* interchangeable signals

EXAMPLE 7

(3S, 4S) 3-hydrazino-4-hydroxymethyl-2-azetidinone (11) from (10).

95.6 mg (288.5 µmoles) of (10), obtained in example 6, were suspended in 1 ml of anhydrous

methylene chloride, under nitrogen stream. The suspension was cooled down to 0°C and 0.5 ml of trifluoroacetic acid were added and a complete dissolution was observed. After 45 minutes, the ice bath was removed and the reaction was let to stand under stirring at r.t. for 1 hour. The solvent was vacuum distilled and the residue was accurately dried at 10^{-2} mm for 24 hours, as to eliminate trifluoroacetic acid completely. The residue pale yellow oil was utilized for the following hydrogenation and for ^{1}H-NMR analysis without purification.

^{1}H-NMR (D_2O, 200 MHz, J(Hz)): δ_H 4.64 (1H, d, J 4.6, H-3), 3.97-4.08 (1H, m, H-4), 3.80-3.91 (2H, m, CH_2OH).

EXAMPLE 8

(3S, 4S) 3-amino-4-hydroxymethyl-2-azetidinone (12) from (11).

The crude, obtained from example 7, was dissolved in 5 ml of water; 50 mg of PtO_2 were added and hydrogenation was carried out at r.t. and atmospheric pressure for 30 hours. The catalyst was filtered off on paper filter, thoroughly washing with water, then with methanol. The solvent was vacuum distilled and the resulting pale-yellow oil was used for next steps and for ^{1}H-NMR analysis without purification.

^{1}H-NMR (D_2O, 200 MHz, J(Hz)): δ_H 4.65 (1H, d, J 5.0, H-3), 4.07-4.12 (1H, m, H-4), 3.92-4.00 (2H, m, CH_2OH).

EXAMPLE 9

(3S, 4S) 3-(benzyloxycarbonylamino)-4-hydroxymethyl-2-azetidinone (13) from (12).

The crude of example 8 was dissolved into 3 ml of 1N $NaHCO_3$ aqueous solution; 64 µl (403.0 µmoles) of

benzyl chloroformate were added and the reaction was let to stand under stirring at r.t. for 6 hours. The suspension was diluted with brine and extracted with ethyl acetate; the organic phase was dried over Na_2SO_4 and vacuum distilled, giving 54 mg of crude, which was subsequently purified by means of colunm chromatography with a 95:5 ethyl acetate/petroleum ether mixture. 36.1 mg (40% yield; three steps) of a white crystalline solid were obtained.

^{1}H-NMR (chloroform-d, 200 MHz, J(Hz)): δ_H 7.33 (5H, s broad, aromatic Cbz), 6.81 (1H, s broad NH-1), 6.27 (1H, d, J 9.9, NH-(Cbz)), 5.14 (1H, dd, J 4.8 e 9.9, H-3), 5.09 (2H, s, CH_2-Ph), 3.80-3.88 (2H, m, CH_2OH), 3.62-3.68 (2H, m, H-4 + OH).

EXAMPLE 10

(3S, 4S) 3-(tert-butoxycarbonylamino)-4-hydroxymethyl-2-azetidinone (14) from (12).

The crude of example 8 was dissolved in 2 ml of anhydrous dimethylformamide, under nitrogen stream, and 115 ml (810 µmoles) of triethylamine and 320 µl (1.35 mmoles) of di-tert-butyl dicarbonate were further added. The reaction system was let to stand for 3 days at r.t. At the end of this time, brine was added followed by extraction with ethyl acetate. The organic phase was dried over Na_2SO_4 and the solvent was vacuum distilled. 63.7 mg of crude were obtained. The subsequent chromatography with a 95:5 ethyl acetate/methanol mixture gave 17.3 mg (30% yield; three steps) of a white solid.

^{1}H-NMR (DMSO-d_6, 200 MHz, J(Hz)): δ_H 8.21 (1H, s, NH-1), 7.31 (1H, d, J 9.8, NH-(Boc)), 4.81 (1H, dd, J 4.1

and 9.8, H-3), 3.32-3.67 (3H, m, H-4 + CH_2OH), 1.39 (9H, s, NH-(Boc)).

EXAMPLE 11

(3S, 4S) 3-(benzyloxycarbonylamino)-4-carbamoyloxymethyl-2-azetidinone (15) from (13).

77.4 mg (309 µmoles) of (13), obtained in example 10, were dissolved in 3.5 ml of a 6:1 methylene chloride/dimethylformamide mixture, under nitrogen stream. The solution was cooled to 0°C and 53 µl (619 µmoles) of chloroacetyl isocyanate were added; the reaction was complete after 1.5 hours. 2.39 mg (1.85 mmoles) of sodium N-methyl dithiocarbamate, previously dissolved into 2 ml of water, were added and the solution was maintained for 4 hours under vigorous stirring, until complete reaction. The aqueous phase was saturated with sodium chloride and extracted with a 85:15 chlorform/methanol mixture. The organic phase was dried over Na_2SO_4 and the solvent was vacuum distilled. The crude was purified through a chromatographic column with a 95:5 ethyl acetate/methanol mixture. 67.9 mg (75% yield; two steps) of a white solid were obtained. ^{1}H-NMR (DMSO-d_6, 200 MHz, J(Hz)): δ_H 8.39 (1H, s, NH-1), 8.00 (1H, d, J 9.5, NH-(Cbz)), 7.36-7.40 (5H, m, Cbz aromatic), 6.56 (2H, s broad, NH_2), 5.01 and 5.10 (2H, AB-system, J 12.5, CH_2-Ph), 4.96 (1H, dd, J 4.8 and 9.5, H-3), 4.10-3.93 (2H, m, CH_2OH), 3.80-3.90 (1H, m, H-4).

EXAMPLE 12

(3S, 4S) 3-(tert-butoxycarbonylamino)-4-carbamoyloxymethyl-2-azetidinone (16) from (14).

The reaction was carried out under the same condi-

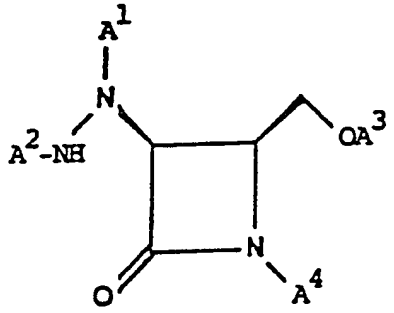
tions described in example 11 and led to the desired product with 63% yield.

^{1}H-NMR (DMSO-d_6, 200 MHz, J(Hz)): δ_H 8.34 (1H, s, NH-1), 7.56 (1H, d, J 9.7, NH-(Boc)), 6.55 (2H, s broad, NH_2), 4.90 (1H, dd, J 5.3 and 9.7, H-3), 3.91-4.12 (2H, m, CH_2OH), 3.76-3.87 (1H, m, H-4), 1.40 (9H, s, NH-(Boc)).

$[\alpha]_D^{18}$ = +56.5° (c 0.75, methanol)

CLAIMS

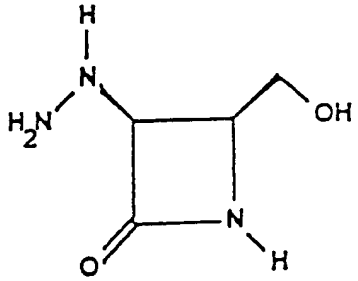
1. (3S, 4S) azetidinones of formula



wherein:

A^1, A^2, A^3, which are the same or different, are hydrogen or nitrogen and oxygen protective groups, and A^4 is hydrogen, hydroxy, or OR^1 group, where R^1 is a methyl or an arylalkyl group; and the organic or inorganic salts thereof, as intermediates.

2. A compound according to claim 1 of formula (11)

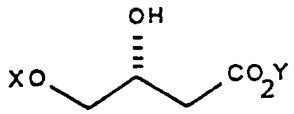


(11)

which is (3S, 4S) 3-hydrazino-4-hydroxymethyl-2-azetidinone, and the inorganic or organic salts thereof.

3. A process for the preparation of (3S, 4S) 3-hydrazino-4-hydroxymethyl-2-azetidinone (11), which consists in

a) condensing (3R) 3-hydroxyesters of formula (4)



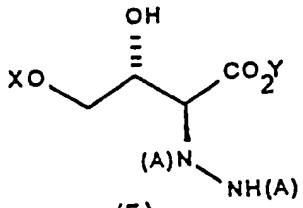
(4)

wherein X is a protective group selected from the group consisting of silyl, triarylmethyl or aryloxymethyl, Y is a C_1-C_3 alkyl group, with an azodicarboxylate of formula

$$A - N = N - A$$

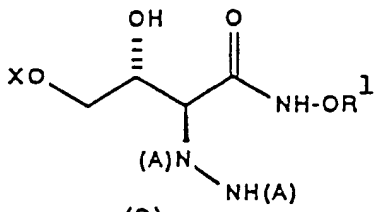
wherein A is a tert-butoxycarboxylate or an arylalkoxycarbonyl group;

b) converting (2S, 3R) 2-N,N'-bis-(A)hydrazino-3-hydroxyesters of formula (5)



(5)

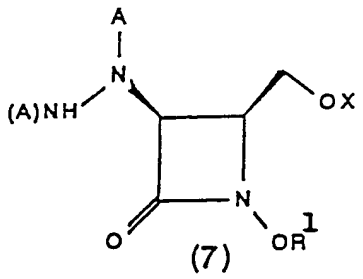
wherein X, Y and A have the above meanings, into the corresponding hydroxamates of formula (6)



(6)

wherein X and A have the above meanings, R^1 is methyl or arylalkyl;

c) cyclizing said hydroxamates (6) into (3S, 4S) azetidinones of formula (7)



(7)

wherein X, A and R^1 have the above meanings;

d) removing X and R^1 groups and reducing the resulting N-OH group to a NH group;

e) removing A groups.

4. A process according to claim 3, characterized in that step a) is carried out by treating hydroxyesters (4) at a temperature ranging from -78°C to +20°C, with at least 2 equivalents of strong base in aprotic solvents and reacting the resulting enolates with an azodicarboxylate at a temperature ranging from -78°C to 0°C.

5. A process according to claim 3, characterized in that step b) is carried out by hydrolizing esters (5) with alkali hydroxydes, at a temperature ranging from 0°C to 60°C, in a system formed by water and a water-miscible solvent, or in an alcoholic system, and reacting the obtained acids with a hydroxylamine of formula NH_2OR^1, where R^1 has the above meanings, in the presence of condensing agents at a temperature ranging from 0°C to 40°C, in aqueous solvent.

6. A process according to claim 3, characterized in that step b) is carried out by reacting esters (5) directly with the adduct obtained from an hydroxylamine of formula NH_2OR^1, where R^1 has the above meanings, with trimethylaluminum in an aprotic solvent, at a tem-

perature ranging from -20°C to the solvent boiling temperature.

7. A process according to claim 3, characterized in that step c) is carried out by reacting hydroxamates (6) with triphenylphosphine and a dialkyl azodicarboxylate in an aprotic solvent, at a temperature ranging from 0°C to 40°C.

8. A process according to claim 3, characterized in that step d), whenever X is a protective group of arylalkylsilyl type, is carried out by removing, in any order X group with fluorides in a solvent selected from the group consisting in tetrahydrofurane, dioxane; and R^1 group with hydrogenolysis on palladium or platinum, and subjecting the azetidinones (9) to the reduction of the OH group with $TiCl_3$ in aqueous CH_3OH.

9. A process according to claim 3, characterized in that step d), whenever X is a protective group of triarylmethyl type and R^1 is arylalkyl, is carried out by removing X wether with protic strong acids in alcoholic solvent at a temperature ranging from 0°C to 60°C, or with aqueous acetic acid at a temperature ranging from 20°C to 100°C, and subsequently removing R^1 by hydrogenolysis on palladium or platinum, and subjecting the azetidinones (9) to the reduction of the OH group with $TiCl_3$ in aqueous CH_3OH.

10. A process according to claim 3, characterized in that step d), whenever X is arylmethoxymethyl and R^1 is arylalkyl, is carried out by contemporaneously removing X and R^1 by hydrogenolysis on palladium or platinum, and subjecting the azetidinones (9) to the reduction of the OH group with $TiCl_3$ in aqueous CH_3OH.

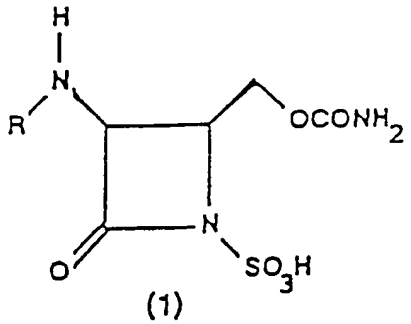
11. A process according to claim 3, characterized in that step d), whenever X is a protective group of silyl type and R^1 is methyl, is carried out by removing X by treating with fluoride in a solvent selected from the group consisting of tetrahydrofurane, dioxane and subsequently reducing the intermediates (8) directly to (10) with alkali metals in liquid ammonia.

12. A process according to claim 3, characterized in that step d), whenever X is triarylmethyl or aryloxymethyl and R^1 is methyl, is carried out by reducing the intermediates (7) directly to (10) with alkali metals in liquid ammonia.

13. A process according to claim 3, characterized in that step e), whenever A is tert-butoxycarbonyl, is carried out with a strong carboxylic acid, optionally in the presence of an inert solvent, at a temperature ranging from 0°C to 25°C.

14. A process according to claim 3, characterized in that steps d) and e), whenever A is arylalkyloxycarbonyl, are carried out at the same time, without isolating the intermediate (10).

15. A process for the preparation of monobactams of formula (1)

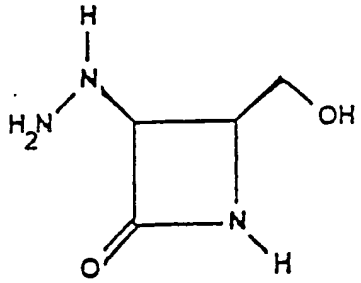


(1)

where R represents an easily removable or pharmaceuti-

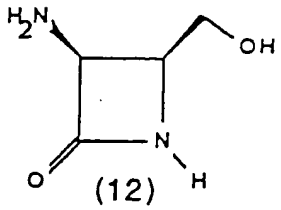
cally acceptable acyl residue, consisting in:

a) converting (3S, 4S) 3-hydrazino-4-hydroxymethyl-2-azetidinone (11)



(11)

into (3S, 4S) 3-amino-4-hydroxymethyl-2-azetidinone (12)



(12)

b) acylating (12) to the corresponding 3-N-acylamino-2-azetidinones;

c) carbamoylating to the corresponding 3-N-acylamino-2-carbamoyloxymethyl-2-azetidinones;

d) sulfamating 3-N-acylamino-4-carbamoyloxymethyl-2-azetidinones to compounds of formula (1).

16. A process according to claim 15, characterized in that step a) is carried out by subjecting (11), or a hydrazinium salt thereof, to catalytic hydrogenation on PtO_2 or Ni Raney®, at a pressure ranging from 1 to 200 atmospheres.

17. A process according to claim 15, characterized in that step b) is carried out by acylating the amino-

derivative (12) with activate derivatives of R-OH acids, where R is as above defined.

18. A process according to claim 15, characterized in that step c), whenever R is benzyloxycarbonyl or tert-butoxycarbonyl, is carried out by treating 3-acylamino-2-azetidinones with an acyl or sulfonyl isocyanate in aprotic solvents and by deprotecting the so obtained N-acyl or N-sulfonyl carbamates with alkali metal N-alkyldithiocarbamates or alkali sulfites, respectively.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/00175

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D205/085

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 111 326 (HOFFMANN-LA ROCHE & CO.) 20 June 1984 see claims	15-18
A	EP,A,0 093 376 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 9 November 1983 cited in the application see claims	15-18
P,A	EP,A,0 411 541 (CONSIGLIO NAZIONALE DELLE RICERCHE) 6 February 1991 see claims	1-18

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06 APRIL 1992	06. 05. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	CHOULY J.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9200175 SA 55448

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/04/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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